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META CHLORO SUBSTITUTED-α-BUTYLAMINO-PROPIOPHENONES

Nariman B. Mehta, Raleigh, N.C., assignor to Burroughs Wellcome Co., Research Triangle Park, N.C.

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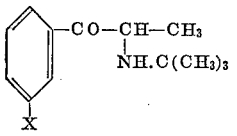
U.S. Cl. 260—570.5 C 6 Claims

ABSTRACT OF THE DISCLOSURE

The compounds *m*-chloro-α-t-butylaminopropiophenone and *m*-fluoro - α - t - butylaminopropionphenone or salts thereof. The compounds are useful in the treatment of mammals suffering from a depressed state.

The present invention relates to α-alkylaminopropiophenones.

It has been found that the two novel compounds represented by the general formula (I)



(I)

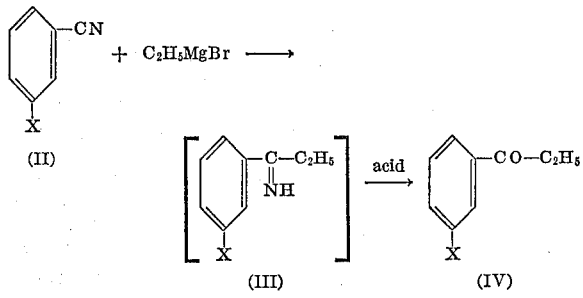
and acid addition salts thereof, in which X is chlorine or fluorine, possess valuable properties as antidepressants when tested by standard techniques used in the art for determining antidepressant activity, for example the tetrabenazine-induced sedation test in rodents. It has been found specifically that the compounds of formula (I) require much larger doses for stimulant action than for antidepressant action. The compounds are also not inhibitors of mono-amine oxidase, nor do they have a pressor effect.

Closely related alkylaminopropiophenones are already known and have been proposed for various pharmaceutical purposes; see for example British Patent Specifications 768,772; 1,011, 289; and 1,069,797. The activity of the two novel compounds of the present invention appears to be outstanding and not possessed by related known compounds.

The compounds may be synthesised by the methods known in the art for this type of compound.

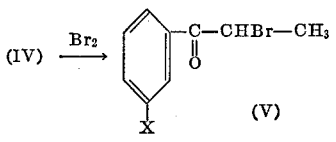
A particularly convenient route is that set out in the following reaction scheme:

(1)



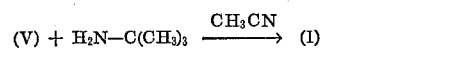
(II) (III) (IV)

(2)



(V)

(3)



The propiophenones, (IV), are not commercially available, and Step (1) has been found a convenient method of preparation. The bromination Step (2), is not very rapid and may require heating. It is not necessary to isolate the ketone (V) as a pure substance provided the hydrogen bromide produced in Step (2) is removed.

It will of course be understood that in Step (3) above, the *m*-X-α-bromopropiophenone (V) may be replaced by the corresponding α-chloro- or α-iodo-compounds. *m*-X-α-Chloropropiophenones may be prepared conveniently by reaction of *m*-X-propiophenone with sulphuryl chloride. The *m*-α-dichloropropiophenone may also be conveniently prepared from α-chloropropiophenone by reaction with sulphuryl chloride in the presence of aluminium chloride. The reaction of Step (3) is subject to hindrance and *t*-butylamine normally reacts very slowly with α-bromopropiophenones. It is desirable to include an organic solvent in the reaction mixture, and for this purpose acetonitrile offers marked advantages. It is a "fast" solvent, is unreactive under the conditions and is relatively low boiling. Other polar solvents, protic or aprotic, may be used, for example lower aliphatic ketones or ethers, but the reaction is slow in these solvents. Others which may be used include dimethylformamide, nitromethane, dimethylsulphoxide and hexamethylphosphoramide.

It is desirable to heat the reactants of Step (3), for example at the reflux temperature of the reaction mixture. The amine is preferably present in excess relative to the ketone; up to five times the equimolar quantity may be used. If the ketone is a *m*-X-α-chloropropiophenone, then a catalytic amount of an iodide salt, for example sodium iodide, may be included in the reaction mixture.

Once isolated the *m*-X-α-t-butylaminopropiophenones of formula (I) are stable and can be distilled *in vacuo* although this is not normally necessary. They are moderately weak bases (pKa around 8.5–9) and are desirably stored and administered as a pharmaceutically acceptable salt, conveniently one of a mineral acid such as the hydrochloride salt. Under physiological conditions, they would be predominantly (but not exclusively) cationic. In any case, if administered as one salt, they would be in equilibrium with the various anions corresponding to other acids present in the body and their salts with different acids can possess advantages only in convenience of isolation or solubility not in inherent physiological behaviour. Accordingly, it is considered that all salts of the bases of formula (I) with non-toxic acids are equivalent to each other and to the bases.

It will be readily understood that salts of acids which are not pharmaceutically acceptable may also have value as intermediates for the preparation of the acceptable salts by double decomposition, base exchange and other well known methods.

According to the present invention there is provided a compound of the formula (I) and a pharmaceutically acceptable salt thereof.

According to the present invention, in yet another aspect, there is provided a pharmaceutical composition (preferably in unit dosage form) comprising a compound of formula (I) (or a pharmaceutically acceptable salt thereof) together with a pharmaceutically acceptable carrier. Conveniently the compound of formula (I) or its acid addition salt comprises from 5 to 95% by weight of the composition.

According to the present invention in yet another aspect there are provided methods of synthesising compounds of formula (I) comprising the application of analogous methods specified above for the preparation of alkylaminopropiophenones.